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The Effects of Extracellular Protons on the hERG Potassium Channel

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The α-subunit of channels mediating the cardiac rapid delayed rectifier current (I_{Kr}) is encoded by the *human Ether-à-go-go-Related Gene* (*hERG*). Macroscopic hERG current (I_{hERG}) amplitude is reduced and deactivation kinetics are accelerated with extracellular acidosis. We have investigated the single channel basis for the effects of acidic external pH (pH_e) on the isoforms of I_{hERG} expressed in myocytes (hERG1a and 1b). Patch clamp recordings were made at room temperature with the extracellular superfusate (whole-cell) or pipette solution (cell attached) acidified to pH 6.3 compared with control (pH 7.4). A decrease in pH_e to 6.3 caused acceleration in deactivation and a reduction in maximal whole-cell conductance of ∼34% for I_{hERG1a} (n=8 cells) and of ∼36% for I_{hERG1b} (n=5 cells). Single channel recordings were made with isotonic potassium (140 mM) bathing the cells and in the electrode. Channel amplitude and open state kinetics were measured at a series of repolarisation voltages following a depolarising command to +40mV. Slope conductance values derived from amplitude current-voltage relationships between −120 and −40mV were 12.3±0.2pS for pH 7.4 (n=10 cells) and 9.3±0.1pS for pH 6.3 (n=9 cells) ($P<0.01$, two-tailed t-test) for hERG1a. The corresponding values for hERG1b were 11.4±0.2pS for pH 7.4 (n=6 cells) and 7.6±0.4pS for pH 6.3 (n=5 cells) ($P<0.0001$; two-tailed t-test). Open-time kinetics at −120mV for hERG1a were reduced from 8.49±1.0ms in control (n=8 cells) to 4.2±0.4ms in pH_e 6.3 (n=7 cells) ($P<0.05$; two-tailed t-test). The hERG1b open state kinetics were 5.7±0.6ms in pH_e 7.4 (n=6 cells) and reduced to 3.1±0.7ms in pH_e 6.3 (n=5 cells) ($P<0.05$; two-tailed t-test). Thus, it can be concluded that a reduction in the single channel conductance and acceleration of open-times contribute to the attenuation of macroscopic I_{hERG} when exposed to acidic pH_e.